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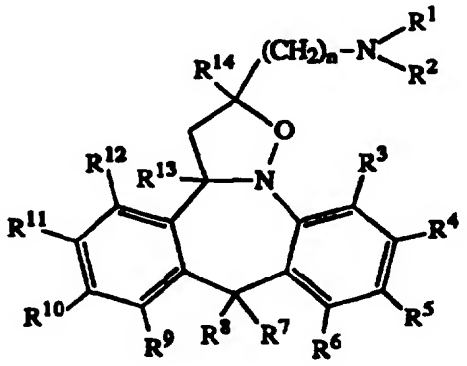
(54) Title: SUBSTITUTED TETRACYCLIC AZEPINE DERIVATIVES WHICH HAVE AFFINITY FOR 5-HT2 RECEPTORS

(57) Abstract

This invention concerns the compounds of formula (I), the pharmaceutically acceptable salts and stereoisomeric forms thereof, and also the *N*-oxide forms thereof. In formula (I) R^1 and R^2 each independently are hydrogen; C_{1-6}alkyl; C_{1-6}alkylcarbonyl; trihalomethylcarbonyl; C_{1-6}alkyl substituted with hydroxy, C_{1-6}alkyloxy, carboxyl, C_{1-6}alkylcarbonyloxy, C_{1-6}alkyloxycarbonyl or aryl; or R^1 and R^2 taken together with the nitrogen atom to which they are attached may form a morpholinyl ring or an optionally substitued heterocycle; R^3, R^4, R^5, R^6, R^9, R^{10}, R^{11} or R^{12} each independently are hydrogen, halo, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, carboxyl, nitro, amino, mono- or di(C_{1-6}alkyl)-amino, C_{1-6}alkylcarbonylamino, aminosulfonyl, mono- or di(C_{1-6}alkyl)-aminosulfonyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxy-carbonyl; R^7 and R^8 are each independently hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy or R^7 and R^8 taken together may form mono- or di(cyano)methylene, or together with the carbon atom to which they are attached form a carbonyl or a spiro substituent; or R^7 and R^8 taken together may form methylene; R^{13} is hydrogen, C_{1-6}alkyl, or trifluoromethyl; R^{14} is hydrogen, C_{1-6}alkyl, cyano, or trifluoromethyl; n is zero to 6. These compounds were tested as mCPP-antagonists in rats. The compounds of formula (I) may be used as therapeutic agents in the treatment or the prevention of CNS disorders, cardiovascular disorders or gastrointestinal disorders.



(I)

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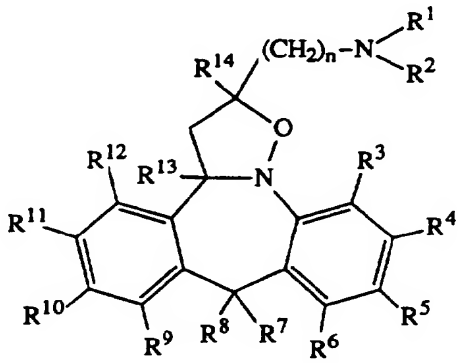
SUBSTITUTED TETRACYCLIC AZEPINE DERIVATIVES WHICH HAVE AFFINITY FOR 5-HT2 RECEPTORS

This invention concerns substituted tetracyclic azepine derivatives having antipsychotic, cardiovascular and gastrokinetic activity and their preparations; it further relates to compositions comprising them, as well as their use as a medicine.

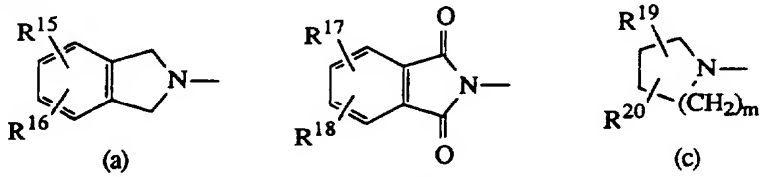
Compounds of similar structure are described in US 4,039,558 which discloses pyrrolidinodibenzo-azepine, -oxazepine, -thiazepine and -diazepine derivatives, having antihistamine, sedative and antidepressant properties. EP-A-0,421,823 describes similar dibenzopyrazino- or benzo-pyrido-pyrazino-azepine derivatives having anti-allergic and anti-asthmatic activities. The present compounds differ therefrom by the presence of an isoxazolidine ring, and by their pharmacological properties.

This invention concerns compounds of formula (I)

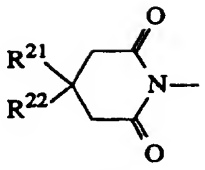


(I)

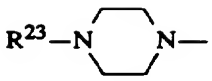
the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof, and also the *N*-oxide forms thereof, wherein :
R^1 and R^2 each independently are hydrogen; C_{1-6}alkyl; C_{1-6}alkylcarbonyl; trihalomethylcarbonyl; C_{1-6}alkyl substituted with hydroxy, C_{1-6}alkyloxy, carboxyl, C_{1-6}alkylcarbonyloxy, C_{1-6}alkyloxycarbonyl or aryl; or R^1 and R^2 taken together with the nitrogen atom to which they are attached may form a morpholinyl ring or a radical of formula :



(a) (b) (c)



(d)



(e)

wherein :

R^{15}, R^{16}, R^{17} and R^{18} each independently are hydrogen, halo, trifluoromethyl, or C_{1-6}alkyl;

m is 1, 2, or 3;

R^{19}, R^{20}, R^{21} and R^{22} each independently are hydrogen, or C_{1-6}alkyl; or R^{21} and R^{22} taken together may form a bivalent radical C_{4-5}alkanediyl;

R^{23} is hydrogen; C_{1-6}alkyl; C_{1-6}alkylcarbonyl; trihalomethylcarbonyl; C_{1-6}alkyloxycarbonyl; aryl; di(aryl)methyl; C_{1-6}alkyl substituted with hydroxy, C_{1-6}alkyloxy, carboxyl, C_{1-6}alkylcarbonyloxy, C_{1-6}alkyloxycarbonyl or aryl;

R^3, R^4, R^5, R^6, R^9, R^{10}, R^{11} and R^{12} each independently are hydrogen, halo, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, carboxyl, nitro, amino, mono- or di(C_{1-6}alkyl)amino, C_{1-6}alkylcarbonylamino, aminosulfonyl, mono- or di(C_{1-6}alkyl)-aminosulfonyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl;

R^7 and R^8 each independently are hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy or R^7 and R^8 taken together may form mono- or di(cyano)methylene; a bivalent radical of formula $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-O-(CH_2)_2-O-$,$-O-(CH_2)_3-O-$; or, together with the carbon atom to which they are attached, a carbonyl; or

R^7 and R^8 taken together may form methylene;

R^{13} is hydrogen, C_{1-6}alkyl or trifluoromethyl;

R^{14} is hydrogen, C_{1-6}alkyl, cyano or trifluoromethyl;

n is zero,1, 2, 3, 4, 5, or 6;

aryl is phenyl; or phenyl substituted with 1, 2 or 3 substituents selected from halo, hydroxy, C_{1-6}alkyl and trifluoromethyl.

In the foregoing definitions C_{1-6}alkyl defines straight and branch chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, 1-methylpropyl, 1,1-dimethylethyl, pentyl, hexyl; C_{4-5}alkanediyl defines bivalent straight and branch chained saturated hydrocarbon radicals having from 4 to 5 carbon atoms such as, for example, 1,4-butanediyl, 1,5-pentanediyl; halo is generic to fluoro, chloro, bromo and iodo. The term monocyanomethylene stands for a radical of formula =CHCN, and dicyanomethylene for

a radical of formula $=C(CN)_2$. In case R^7 and R^8 taken together form a bivalent radical as defined above, the compounds of formula (I) are spiro compounds.

The pharmaceutically acceptable acid addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. Said salts can be obtained by treating the base form of the compounds of formula (I) with appropriate acids such as inorganic acids, for example, hydrohalic acid, e.g. hydrochloric or hydrobromic, sulfuric, nitric, phosphoric and the like acids; or organic acids, such as, for example, acetic, hydroxyacetic, propanoic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

Suitable acids are oxalic acid, in particular (R)- or (S)-malic acid and fumaric acid; especially (S)-malic acid.

The compounds of formula (I) containing acidic protons may also be converted into their therapeutically active non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

Conversely said salt forms can be converted into the free forms by treatment with an appropriate base or acid.

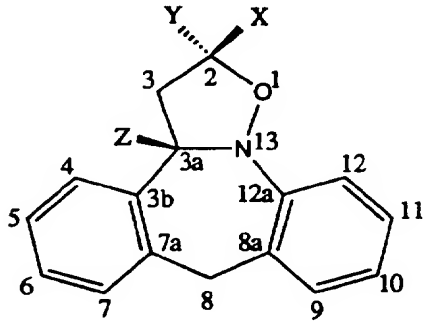
The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

The *N*-oxide forms of the compounds of formula (I) are meant to comprise those compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide, particularly those *N*-oxides wherein the nitrogen bearing the R^1 and R^2 substituents is *N*-oxidized.

The term "stereochemically isomeric forms" as used hereinbefore and hereinafter defines all the possible isomeric forms in which the compounds of formula (I) may occur. Unless otherwise mentioned or indicated, the chemical designation of compounds

denotes the mixture, and in particular the racemic mixture, of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. Stereochemically isomeric forms of the compounds of formula (I) and mixtures of such forms are obviously intended to be encompassed by formula (I).

The numbering of the tetracyclic ring-system present in the compounds of formula (I), as defined by Chemical Abstracts nomenclature is shown in formula (I').



(I')

The compounds of formula (I) occur as "*cis*" and "*trans*" isomers. Said terms refer to the position of the substituents on the isoxazolidine ring and are in accordance with Chemical Abstracts nomenclature. The nomenclature is unusual in that carbon atom 3b, being part of a cyclic system, is not considered as a relevant substituent of carbon atom 3a. When establishing the configuration, the substituent on carbon atom 3a (i.e. "Z") and the substituent with the highest priority on carbon atom 2 (i.e. either "X" or "Y") are considered. When "Z" and the substituent with the highest priority on carbon atom 2 are on the same side of the mean plane determined by the isoxazolidine ring then the configuration is designated "*cis*", if not, the configuration is designated "*trans*".

The compounds of formula (I) have at least two asymmetric centers, namely carbon atom 3a bearing the substituent R^{13} and carbon atom 2 bearing the substituent R^{14}. Said asymmetric centers and any other asymmetric center which may be present, are indicated by the descriptors R and S. When a monocyanomethylene moiety is present in the compounds of formula (I), said moiety may have the E- or Z-configuration.

Of some compounds of formula (I) the absolute stereochemical configuration was not experimentally determined. In those cases the stereochemically isomeric form which was first isolated is designated as "A" and the second as "B", without further reference to the actual stereochemical configuration.

Whenever used hereinafter, the term compounds of formula (I) is meant to also include the pharmaceutically acceptable acid addition salts, base addition salts and all stereoisomeric forms, and also the *N*-oxide forms.

Particular groups of compounds of formula (I) are those wherein one or more of the following restrictions apply :

a) R^1 and R^2 each independently are hydrogen, C_{1-6}alkyl, trihalomethylcarbonyl, C_{1-6}alkyl substituted with hydroxy, carboxyl, C_{1-6}alkylcarbonyloxy; or R^1 and R^2 taken together with the nitrogen atom to which they are attached form a radical of formula (a) in which R^{15} and R^{16} are both hydrogen, a radical of formula (b) in which R^{17} and R^{18} are both hydrogen, a radical of formula (c) in which R^{19} and R^{20} are both hydrogen, a radical of formula (d) in which R^{21} and R^{22} taken together form a C_{4-5}alkanediyl radical, or a radical of formula (e) in which R^{23} is hydrogen, C_{1-6}alkyl, trihalomethylcarbonyl or aryl;

b) R^3, R^4, R^5 and R^6 each independently are hydrogen, halo, C_{1-6}alkyl, or trifluoromethyl;

c) R^9, R^{10}, R^{11} and R^{12} each independently are hydrogen, halo, C_{1-6}alkyl, or trifluoromethyl;

d) R^7 and R^8 both are methyl, or in particular hydrogen;

e) R^{13} is methyl, or in particular hydrogen;

f) R^{14} is methyl or cyano, or in particular is hydrogen;

g) n is 1, 2, 3 or 4; and particularly is 1;

h) R^3, R^4, R^5 and R^6 each independently are C_{1-6}alkyloxy or mono- or di(C_{1-6}alkyl)-amino;

i) R^9, R^{10}, R^{11} and R^{12} each independently are C_{1-6}alkyloxy or mono- or di(C_{1-6}alkyl)amino;

j) R^7 is methyl and R^8 is hydrogen; or R^7 and R^8 taken together form methylene or cyanomethylene;

k) R^1 and R^2 taken together with the nitrogen atom to which they are attached form a radical of formula (e) in which R^{23} is di(aryl)methyl.

Of special interest are those compounds of formula (I) or subgroups as defined above, wherein one of the aromatic substituents R^3, R^4, R^5, R^6, R^9, R^{10}, R^{11}, R^{12} is selected from hydrogen, halo, C_{1-6}alkyl, or trifluoromethyl; the remaining aromatic substituents being hydrogen.

Also of special interest are those compounds of formula (I) or subgroups as defined above, wherein two or more of the aromatic substituents R^3, R^4, R^5, R^6, R^9, R^{10}, R^{11}, R^{12} are selected from fluoro, chloro or bromo; the remaining aromatic substituents being hydrogen.

More interesting are those compounds of special interest wherein the aromatic substituents R^4, R^5 and R^{11} each independently are selected from hydrogen, fluoro, chloro, bromo, methyl or trifluoromethyl; the remaining aromatic substituents being hydrogen.

Preferred compounds are those compounds of formula (I) or subgroups of compounds of formula (I) as defined above, wherein R^1 and R^2 are both methyl and n is 1 or 2.

Also preferred are those compounds of formula (I) or subgroups of compounds of formula (I) as defined above, wherein R^1 is hydrogen, R^2 is methyl and n is 1 or 2.

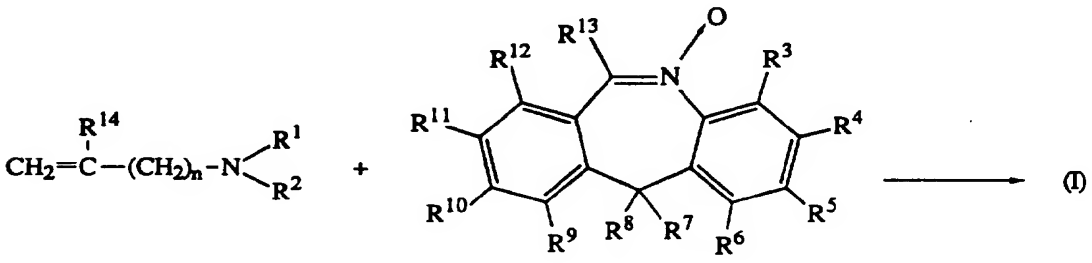
The most preferred compounds are :
cis-2,3,3a,8-tetrahydro-*N*,*N*-dimethyldibenz[c,f]isoxazolo[2,3-a]azepine-2-methanamine, the stereochemically isomeric forms and pharmaceutically acceptable acid addition salts thereof, and also the *N*-oxide forms thereof.

Further most preferred are the compounds :
cis-2,3,3a,8-tetrahydro-*N*-methyldibenz[c,f]isoxazolo[2,3-a]azepine-2-methanamine, the stereochemically isomeric forms and pharmaceutically acceptable acid addition salts thereof, and also the *N*-oxide forms thereof.

Among the most preferred compounds mentioned hereinabove, (+)-(A-*cis*)-2,3,3a,8-tetrahydro-*N*,*N*-dimethyldibenz[c,f]isoxazolo[2,3-a]azepinemethanamine (S)-hydroxybutanedioate(1:1) is specifically preferred.

Interestingly, the compounds of formula (I) are fairly simple to synthesise. In general, they may be prepared by a 1,3-dipolar cycloaddition of a dienophile of formula (III) and an intermediate of formula (II). In the intermediates (II) and (III) and in any other intermediate mentioned hereinunder, R^1 to R^{14} and n are as defined hereinabove, unless otherwise indicated. Said 1,3-dipolar cycloaddition may conveniently be carried out by

mixing the reactants, optionally in a reaction-inert solvent such as, for example, an aromatic solvent, e.g. toluene; a ketone, e.g. 4-methyl-2-pentanone; or a mixture of such solvents. Stirring and elevated temperatures, or increased pressure may enhance the rate of the reaction. The reaction of intermediate (II) with intermediate (III) in practice is regioselective yielding to compounds of formula (I).



(III) (II) (I)

In this and the following preparations, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, trituration and chromatography.

The compounds of formula (I) may also be converted into each other following art-known transformations. For example,

a) a compound of formula (I), wherein R^1 and R^2 taken together with the nitrogen atom to which they are attached form a radical of formula (b), may be converted into the corresponding primary amine by treatment with hydrazine or aqueous alkali;

b) a compound of formula (I), wherein R^1 or R^2 is trifluoromethylcarbonyl, may be converted into the corresponding primary or secondary amine by hydrolysis with aqueous alkali;

c) a compound of formula (I), wherein R^1 or R^2 is C_{1-6}alkyl substituted with C_{1-6}alkyl-carbonyloxy may be hydrolyzed into a compound of formula (I) wherein R^1 or R^2 is C_{1-6}alkyl substituted with hydroxy;

d) a compound of formula (I), wherein R^1 and R^2 are both hydrogen may be mono- or di-*N*-alkylated to the corresponding amine form;

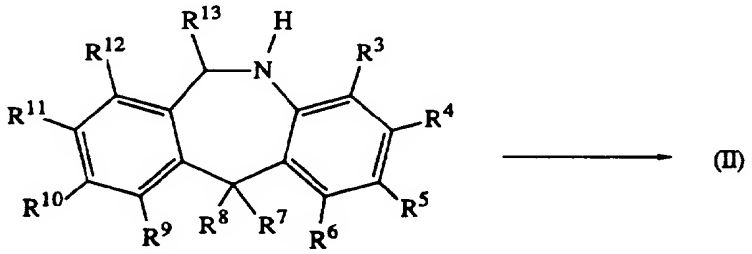
e) a compound of formula (I), wherein R^1 and R^2 are both hydrogen may be *N*-acylated to the corresponding amide;

f) a compound of formula (I), containing a C_{1-6}alkyloxycarbonyl group may be hydrolyzed to the corresponding carboxylic acid.

The compounds of formula (I) may also be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its

N-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with 3-phenyl-2-(phenylsulfonyl)oxaziridine or with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. t-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

The intermediates of formula (II) may be prepared by the oxidation of an intermediate of formula (IV) with a suitable oxidizing agent such as, for example, 2-benzenesulfonyl-3-phenyl-oxaziridine, hydrogen peroxide, *t*-butyl hydroxyperoxide, or metachloroperbenzoic acid.

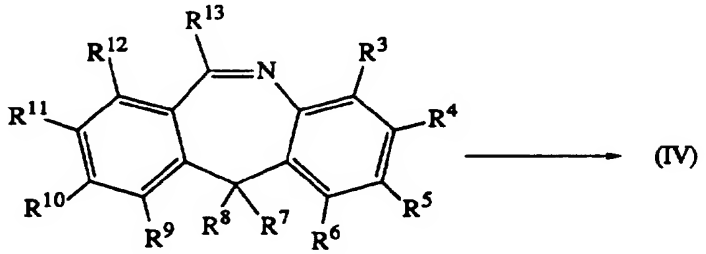


(IV)

Said oxidation is performed in a reaction-inert solvent at temperatures ranging between -20°C and 50°C, preferably between 0°C and room temperature. Suitable solvents are, for example, water; chlorinated hydrocarbons, e.g. dichloromethane or chloroform; aromatic hydrocarbons, e.g. toluene; alcohols such as methanol; ketones, e.g. 4-methyl-2-pentanone; or a mixture of such solvents. When using peroxide oxidants, the reaction rate may be enhanced by using metallic catalysts such as, for example, Na_2WO_4, $VO(acetylacetonate)_2$, $Ti(OBu)_4$, or $MoO_2(acetylacetonate)_2$, optionally under a reaction-inert atmosphere such as, for example, argon.

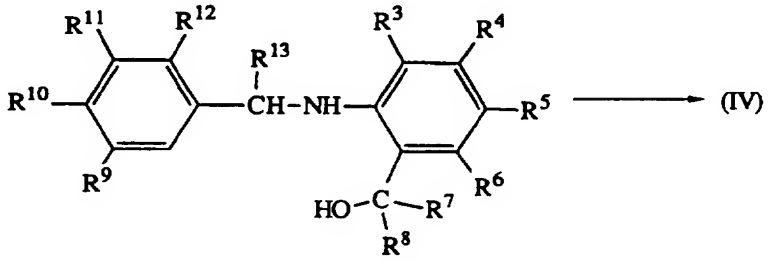
Intermediates of formula (IV) may be formed by the reduction of an imine of formula (V) with hydrogen in combination with a suitable catalyst such as, for example, palladium or platinum supported on for instance charcoal; in a reaction-inert solvent such as, for

example, tetrahydrofuran, methanol or a mixture of such solvents. The formation of an imine of formula (V) is disclosed in J. Chem. Soc. Perk. I (1976), 1279.



(V) (IV)

Intermediates of formula (IV) may also be prepared by an intramolecular cyclization of an intermediate of formula (VI) by adding a strong acid such as, for example, sulfuric acid or phosphoric acid, optionally in a reaction-inert solvent, to an intermediate of formula (VI).



(VI) (IV)

Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereomers may be separated by physical methods such as selective crystallization and chromatographic techniques, e.g. counter-current distribution, liquid chromatography and the like.

The compounds of formula (I) as prepared in the hereinabove described processes are generally racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of formula (I) which are sufficiently basic or acidic may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid such as, for example, di-1,4-toluolyl-D-tartaric acid, respectively with a suitable chiral base. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali or acid. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure

stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The compounds of the present invention show affinity for 5-HT_2 receptors, particularly for 5-HT_{2A} and 5-HT_{2C} receptors (nomenclature as described by D. Hoyer in "Serotonin (5-HT) in neurologic and psychiatric disorders" edited by M.D. Ferrari and published in 1994 by the Boerhaave Commission of the University of Leiden). Furthermore, the compounds of the present invention show interesting pharmacological activity in the "mCPP Test on Rats" which is described hereinafter and in the "Elevated and Illuminated Plus Maze Test" which is described in Drug Dev. Res. 18, 119-144 (1989). Additionally, the present compounds show interesting pharmacological activity in the "Tail Suspension Test", the "Combined Apomorphine, Tryptamine, Norepinephrine (ATN) Test on Rats" which is described in Arch. Int. Pharmacodyn, 227, 238-253 (1977), and also in the "LSD Drug Discrimination Test" which is described in Drug Dev. Res. 18, 119-144 (1989). Another interesting property of the compounds of formula (I) is that they suppress amphetamine-induced stereotypical behaviour in rats.

In view of these pharmacological properties, the compounds of formula (I) are useful as therapeutic agents in the treatment or the prevention of central nervous system disorders like anxiety, depression and mild depression, bipolar disorders, sleep- and sexual disorders, psychosis, borderline psychosis, schizophrenia, migraine, personality disorders or obsessive-compulsive disorders, social phobias or panic attacks, organic mental disorders, mental disorders in children, aggression, memory disorders and attitude disorders in older people, addiction, obesity, bulimia and similar disorders. In particular, the present compounds may be used as anxiolytics, antidepressants and as agents having the potential to overrule the addictive properties of drugs of abuse.

The compounds of formula (I) may also be used as therapeutic agents in the treatment of motoric disorders. It may be advantageous to use the present compounds in combination with classical therapeutic agents for such disorders.

The compounds of formula (I) may also serve in the treatment or the prevention of damage to the nervous system caused by trauma, stroke, neurodegenerative illnesses and the like; cardiovascular disorders like high blood pressure, thrombosis, stroke, and the like; and gastrointestinal disorders like dysfunction of the motility of the gastrointestinal

system and the like. The present compounds may also be useful as anticonvulsive agents.

In view of the above uses of the compounds of formula (I), it follows that the present invention also provides a method of treating warm-blooded animals suffering from such diseases, said method comprising the systemic administration of a therapeutic amount of a compound of formula (I) effective in treating the above described disorders.

The present invention thus also relates to compounds of formula (I) as defined hereinabove for use as a medicine, in particular for use as medicine to treat the above described disorders.

Those of skill in the treatment of such diseases could determine the effective therapeutic daily amount from the test results presented hereinafter. An effective therapeutic daily amount would be from about 0.001 mg/kg to about 10 mg/kg body weight, more preferably from about 0.005 mg/kg to about 1 mg/kg body weight.

For ease of administration, the subject compounds may be formulated into various pharmaceutical forms for administration purposes. To prepare the pharmaceutical compositions of this invention, a therapeutically effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable solutions containing compounds of formula (I) may be formulated in an oil for prolonged action. Appropriate oils for this purpose are, for example, peanut

oil, sesame oil, cottonseed oil, corn oil, soy bean oil, synthetic glycerol esters of long chain fatty acids and mixtures of these and other oils. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wettable agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause any significant deleterious effects on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on or as an ointment. Acid or base addition salts of compounds of formula (I) due to their increased water solubility over the corresponding base or acid form, are obviously more suitable in the preparation of aqueous compositions.

In order to enhance the solubility and/or the stability of the compounds of formula (I) in pharmaceutical compositions, it can be advantageous to employ α–, β– or γ-cyclodextrins or their derivatives, in particular hydroxyalkyl substituted cyclodextrins, e.g. 2-hydroxypropyl-β-cyclodextrin. Also co-solvents such as alcohols may improve the solubility and/or the stability of the compounds of formula (I) in pharmaceutical compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect, in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

The following examples are intended to illustrate and not to limit the scope of the present invention.

Experimental part

Hereinunder, "DIPE" means diisopropylether, and "EtOAc" means ethylacetate.

A. Preparation of the intermediates

Example 1

Trifluoroacetic acid anhydride (12.7 ml) was added dropwise at 0°C to a solution of *N*-methyl-2-propen-1-amine (5 g) and triethylamine (14.7 ml) in diethylether (50 ml) and this mixture was stirred at room temperature for 6 hours. after which the solvent was evaporated. The residue was dissolved in water, extracted with CH_2Cl_2 and the solvent evaporated, yielding 9.4 g (75%) of 2,2,2-trifluoro-*N*-methyl-*N*-2-propenylacetamide (interm. 1).

Analogously, 1-(2-propenyl)-4-(trifluoroacetyl)piperazine (interm. 2) was prepared.

Example 2

a) A mixture of *N*-methyl-2-propen-1-amine (2.7 ml), ethyl 3-bromo-propanoate (4.5 ml) and potassium carbonate (5.8 g) in 2-butanone (20 ml) was stirred at 50 °C for 4 hours. The mixture was cooled to room temperature, filtered and the filtrate evaporated. The residue was dissolved in water, extracted with CH_2Cl_2 and the solvent evaporated. The residue was purified by column chromatography over silica gel (eluent : CH_2Cl_2/CH_3OH 9.75/0.25). The pure fractions were collected and evaporated, yielding 3 g (63%) of ethyl *N*-methyl-*N*-2-propenyl-β-alanine (interm. 3).

Similarly, the following intermediates were prepared :

ethyl 4-[methyl(2-propenyl)amino]butanoate (interm. 4);

ethyl 5-[methyl(2-propenyl)amino]pentanoate (interm. 5); and

2-[methyl(2-methyl-2-propenyl)amino]ethanol acetate(ester) (interm. 81).

b) A mixture of intermediate 4 (14 g) in a hydrochloric acid solution (35%) (38 ml), acetic acid (38 ml) and water (19 ml) was stirred and refluxed for 5 hours. The mixture was cooled on an ice bath and NaOH (50%) was added until the pH was about 6 after which the solvent was evaporated. The residue was washed with CH_2Cl_2. The precipitate was filtered off and the filtrate evaporated. The syrup (19.4 g) was washed with toluene and the solvent was evaporated. The product was used without further purification, yielding 15 g (100%) of 4-[methyl(2-propenyl)amino]butanoic acid (interm. 6).

Analogously, 5-[methyl(2-propenyl)amino]pentanoic acid (interm. 7) was prepared from intermediate 5.

Example 3

A mixture of 5-hexen-1-ol (5 g) and 8-azaspiro[4.5]decane-7,9-dione (14 ml) in triethylamine (150 ml) was cooled on an ice bath. Methane-sulfonyl chloride (8.6 g) in triethylamine (50 ml) was added dropwise and the mixture was stirred at room temperature for 1 hour. The mixture was filtered off and the filtrate evaporated. Dichloromethane (7.7 g), potassium carbonate (7.6 g) and *N,N*-dimethylformamide (100 ml) were added to the residue and the mixture was stirred at 160 °C overnight. The

mixture was filtered off and the filtrate evaporated. The residue was purified by short open column chromatography over silica gel (eluent : CH_2Cl_2/CH_3OH 100/0 to 98/2). The pure fractions were collected and evaporated, yielding 1.5 g (13%) of 8-(5-hexenyl)-8-azaspiro[4.5]decane-7,9-dione (interm. 8).

Example 4

a) P_2O_5 (516.5 g) was added portionwise to H_3PO_4 (247.5 ml) and stirred under a N_2 flow at room temperature. The mixture was stirred for 2 hours at 120 °C, then cooled to 50 °C. *p*-Xylene (1810 ml) was added, and stirring was continued for 15 minutes. $POCl_3$ (83.3 g) was added, and stirring was continued for 10 minutes. *N*-[2-(phenylmethyl)phenyl]formamide (prepared as described in Helv. Chim. Acta 47(5) 1163-72 (1964)) (37.2 g) was added portionwise. The mixture was stirred for 30 minutes at 60-70 °C. Another portion of *N*-[2-(phenylmethyl)phenyl]formamide (74.3 g) was added portionwise, and the reaction mixture was stirred overnight at 100 °C. The reaction mixture was cooled and the *p*-xylene layer was removed. Water (990 ml) was added slowly. The mixture was cooled with ice-water. A solution of KOH (1073 g) in water (2200 ml) was added over 2 hours. CH_2Cl_2 (500 ml) was added dropwise and the mixture was stirred vigorously during 15 minutes. The organic layer was separated. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$, filtered off and the solvent evaporated. The residue was purified by distillation yielding a mixed fraction. The mixed fraction was repurified twice by distillation, yielding 1.4 g of 11*H*-dibenz[b,e]azepine (interm. 9).

b) A mixture of intermediate 9 (116 g) in methanol (1000 ml) was hydrogenated with palladium on activated carbon (10%) (17.7 g) as a catalyst. After uptake of hydrogen (1 eq.), the catalyst was filtered off and the filtrate evaporated. The residue was stirred up in DIPE (80%), the precipitate was filtered off and dried in vacuo at 45 °C for 24 hours, yielding 88.1 g (75.7%) of 6,11-dihydro-5*H*-dibenz[b,e]-azepine (interm. 10).

In a similar way, there were prepared :

3-chloro-6,11-dihydro-5*H*-dibenz[b,e]azepine (interm. 11); and

2-chloro-6,11-dihydro-5*H*-dibenz[b,e]azepine (interm. 12).

c) Bromine (1.3 ml) was added dropwise to a mixture of intermediate 10 (5 g) in acetic acid (12 ml) and the mixture was stirred at room temperature for 4 hours. The solvent was evaporated and the residue was washed with NH_4OH (10%) and dissolved in CH_2Cl_2. The organic layer was dried with Na_2SO_4, filtered off and evaporated. The residue (8 g) was purified by flash chromatography over silica gel (eluent : hexane/EtOAc 9/1). The pure fractions were collected and evaporated, yielding 4 g (56%) of 2 bromo-6,11-dihydro-5*H*-dibenz[b,e]azepine (interm. 13).

Example 5

a) 2-amino-6-chlorobenzoic acid (25 g) dissolved in acetic anhydride (100 ml) was stirred at 120 °C for 2 hours. The mixture was cooled to room temperature and filtered off. The precipitate was washed with water and Na_2CO_3 (10%) and dissolved in CH_2Cl_2. The solution was dried with Na_2SO_4, filtered off and evaporated. The residue was crystallized twice from benzene, yielding 13 g (46%) of 5-chloro-2-methyl-4*H*-3,1-benzoxazin-4-one; mp. 148.7°C (interm. 14).

b) Intermediate 14 (20 g) was dissolved in tetrahydrofuran (200 ml) and the mixture was cooled on an ice water bath under a N_2 atmosphere. Phenylmagnesium bromide (34 ml) in tetrahydrofuran (100 ml) was added dropwise and the mixture was stirred at 10 °C for 1 hour. The mixture was quenched with water and HCl (2N) and extracted twice with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4, filtered off and the filtrate evaporated. The residue was purified by short open column chromatography over silica gel (eluent : CH_2Cl_2). The pure fractions were collected and evaporated, yielding 24.5 g (87%) of *N*-(2-benzoyl-3-chlorophenyl)-acetamide (interm. 15).

c) Intermediate 15 (20 g) dissolved in acetic acid (700 ml) and hydrochloric acid (175 ml) was stirred and refluxed for 6 hours. The mixture was cooled to room temperature and the solvent evaporated. The residue was partitioned between CH_2Cl_2 and Na_2CO_3 10%. The organic layer was dried with Na_2SO_4, filtered off and evaporated. The residue was crystallized from DIPE/EtOAc, yielding 10.5 g (62%) of (2-amino-6-chlorophenyl)phenylmethanone; mp. 191.5°C (interm. 16).

d) Intermediate 16 (10.5 g) and hydrazine hydrate (8.8 ml) were dissolved in 1,2-ethanediol (200 ml) and the mixture was stirred at 200°C for 2 hours. The mixture was cooled to 60°C, KOH (5.1 g) was added and the mixture was stirred at 200°C overnight. The mixture was cooled to room temperature and partitioned between water and CH_2Cl_2. The organic layer was dried with Na_2SO_4, filtered off and evaporated, yielding 9 g (90%) of 3-chloro-2-(phenylmethyl)-benzenamine (interm. 17).

e) A mixture of intermediate 17 (10 g) dissolved in formic acid (100 ml) was stirred and refluxed for 2 hours. The mixture was cooled to room temperature and the solvent evaporated. Na_2CO_3 (10%) was added to the residue and this aqueous mixture was extracted twice with CH_2Cl_2. The organic layer was dried with Na_2SO_4, filtered off and evaporated, yielding 9.6 g (85%) of *N*-[3-chloro-2-(phenylmethyl)phenyl]formamide (interm. 18).

f) Starting from intermediate 18, 1-chloro-6,11-dihydro-5*H*-dibenz[b,e]azepine (interm. 19) was prepared following the procedures as described in example 4.

Analogously, 6,11-dihydro-4-methyl-5*H*-dibenz[b,e]azepine (interm. 20) was prepared.

Example 6

a) A solution of 3-bromobenzenamine (20 g) in 1,2-dichloroethane was added dropwise under a N_2 atmosphere to a solution of BCl_3/xylene (128 ml) in 1,2-dichloroethane cooled on ice. Cyanobenzene (12 g) in 1,2-dichloroethane and $AlCl_3$ (17 g) were also added and the mixture was stirred and refluxed overnight. The mixture was cooled, ice/HCl (2N) was added while stirring and the mixture was stirred and heated at 80°C for 30 minutes. The mixture was cooled, diluted with water and extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4, filtered off and evaporated. The residue was purified by short open column chromatography over silica gel (eluent : hexane/ CH_2Cl_2/EtOAc 6/3/1). The pure fractions were collected and evaporated, yielding 13 g (41%) of (4-bromo-2-aminophenyl)phenyl-methanone (interm. 21).

b) Starting from intermediate 21, 3-bromo-6,11-dihydro-5*H*-dibenz[b,e]azepine (interm. 22) was prepared in an analogous manner as intermediate 19 was prepared from intermediate 16 as described in example 5d, 5e and 5f.

Analogously, there were prepared :

6,11-dihydro-3-methyl-5*H*-dibenz[b,e]azepine (interm. 23);

6,11-dihydro-2-methyl-5*H*-dibenz[b,e]azepine (interm. 24);

6,11-dihydro-10-methyl-5*H*-dibenz[b,e]azepine (interm. 25); and

6,11-dihydro-8-methyl-5*H*-dibenz[b,e]azepine (interm. 26).

Example 7

2-[[(4-chlorophenyl)methyl]amino]benzenemethanol (6.7 g) (prepared as described in J. Chem. Soc. Chem. Commun., 1989 (1), 44-5) was cooled under a N_2 atmosphere to -40°C. Sulfuric acid (35 ml) was added dropwise keeping the temperature at about -10°C and the mixture was stirred at room temperature for 1 hour. The mixture was poured into ice water and basified carefully with KOH. The mixture was filtered off and the precipitate was washed with water and CH_2Cl_2. The filtrate and the washings were extracted, dried with Na_2SO_4, filtered off and evaporated, yielding 5.8 g (95%) of 9-chloro-6,11-dihydro-5*H*-dibenz-[b,e]azepine (interm. 27).

Analogously, 3-fluoro-6,11-dihydro-5*H*-dibenz[b,e]azepine (interm. 28) was prepared.

Example 8

Procedure 1

3-Phenyl-2-(phenylsulfonyl)oxaziridine (18.7 g) was added portionwise to a solution of intermediate 10 (7 g) in $CHCl_3$ (120 ml) and was subsequently stirred at room temperature for 2 hours. The solvent was evaporated and the residue was purified by short open column chromatography over silica gel (eluent : CH_2Cl_2/CH_3OH 97.5/2.5).

The pure fractions were collected and evaporated, yielding 10 g (80%) of 11*H*-dibenz[b,e]azepine,5-oxide; mp. 109.2°C (interm. 29).

Procedure 2

A solution of intermediate 10 (50 g) in CH_2Cl_2 (1282 ml) was stirred and cooled to ± 10°C. A solution of metachloroperbenzoic acid (115.6 g) in CH_2Cl_2 (2430 ml) was added dropwise at < 15 °C. The reaction mixture was stirred for 1 hour. The mixture was extracted with a 10% aqueous Na_2SO_3 solution (1 liter), then with a 5% aqueous Na_2CO_3 solution. The organic phase was dried, filtered, and the solvent was evaporated, yielding 53.5 g (quantitative yield) of 11*H*-dibenz[b,e]azepine,5-oxide (interm 29).

Analogous to procedure 2, the following intermediates were prepared :

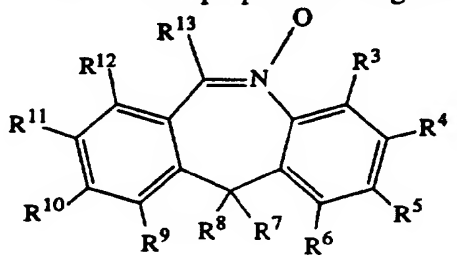
11-methylene-11*H*-dibenz[b,c]azepine,5-oxide (interm. 73);

2,3-dimethyl- 11*H*-dibenz[b,c]azepine,5-oxide (interm. 74); and

3-chloro-2-methyl-11*H*-dibenz[b,c]azepine,5-oxide (interm. 75).

The compounds listed in Table 1 were prepared analogously to procedure 1.

Table 1



Int. No.	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}	R^{12}	R^{13}	physical data (mp. in °C)
29	H	H	H	H	H	H	H	H	H	H	H	109.2
30	H	Cl	H	H	H	H	H	H	H	H	H	-
31	H	H	Cl	H	H	H	H	H	H	H	H	-
32	H	H	H	Cl	H	H	H	H	H	H	H	-
33	H	Br	H	H	H	H	H	H	H	H	H	-
34	CH_3	H	H	H	H	H	H	H	H	H	H	-
35	H	CH_3	H	H	H	H	H	H	H	H	H	-
36	H	H	CH_3	H	H	H	H	H	H	H	H	-
37	H	H	H	H	H	H	CH_3	H	H	H	H	-
38	H	H	H	H	H	H	H	H	CH_3	H	H	-
39	H	H	H	H	H	H	H	Cl	H	H	H-	-
40	H	F	H	H	H	H	H	H	H	H	H	-
41	H	H	Br	H	H	H	H	H	H	H	H	-
42	H	H	H	H	H	H	H	H	H	H	CH_3	141.7

Int. No	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}	R^{12}	R^{13}	physical data (mp. in °C)
43	H	H	H	H	CH_3	CH_3	H	H	H	H	H	-
44	H	H	H	CH_3	H	H	H	H	H	H	H	-
45	H	H	H	H	CH_3	H	H	H	H	H	H	-
46	H	H	H	F	H	H	H	H	H	H	H	-
47	H	H	H	H	H	H	F	H	H	H	H	-
48	H	H	H	H	H	H	H	F	H	H	H	-
49	H	H	H	H	H	H	H	H	F	H	H	-
50	H	H	H	H	H	H	H	H	H	F	H	-
51	H	H	H	H	H	H	H	CF_3	H	H	H	-
52	H	H	H	H	H	H	H	H	H	CF_3	H	-
53	H	H	H	H	H	H	Cl	H	H	H	H	-
54	H	H	H	H	H	H	H	H	Cl	H	H	-
55	H	Cl	Cl	H	H	H	H	H	H	H	H	-
56	H	Cl	H	H	H	H	Cl	H	H	H	H	-
57	H	Cl	H	H	H	H	H	H	Cl	H	H	-
58	H	Cl	F	H	H	H	H	H	H	H	H	-
59	H	F	H	H	H	H	Cl	H	H	H	H	-
60	H	F	H	H	H	H	H	H	Cl	H	H	-
61	H	F	H	H	H	H	F	H	H	H	H	-
62	H	F	H	H	H	H	H	H	F	H	H	-
63	H	Cl	H	H	H	H	Cl	Cl	H	H	H	-
64	H	Cl	H	H	H	H	H	Cl	Cl	H	H	-
65	H	H	H	Br	H	H	H	H	H	H	H	-
66	H	H	H	H	H	H	Br	H	H	H	H	-
67	H	H	H	H	H	H	H	Br	H	H	H	-
68	H	H	H	H	H	H	H	H	Br	H	H	-
69	H	OCH_3	H	H	H	H	H	H	H	H	H	-
70	H	H	H	OCH_3	H	H	H	H	H	H	H	-
71	H	H	H	H	H	H	H	H	OCH_3	H	H	-
72	H	H	H	H	H	H	H	$N(CH_3)_2$	H	H	H	-
76	H	Cl	Cl	H	H	H	H	H	CH_3	H	H	-
77	H	F	F	H	H	H	H	H	H	H	H	-

Int. No	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}	R^{12}	R^{13}	physical data (mp. in °C)
78	H	H	H	H	CH_3	H	H	H	H	H	H	(A)
79	H	H	H	H	CH_3	H	H	H	H	H	H	(B)
80	H	F	Cl	H	H	H	H	H	H	H	H	-

B. Preparation of compounds of formula (I)

Example 9

A mixture of intermediate 29 (2.7 g) and *N,N*-dimethyl-2-propen-1-amine (3 ml) in toluene (60 ml) was stirred at 100°C overnight. The solvent was evaporated and the residue was purified by flash chromatography over silica gel (eluent : CH_2Cl_2/CH_3OH 95/5). The pure fractions were collected and evaporated. The residue (3.1 g), containing the free base (±)-*cis*-2,3,3a,8-tetrahydro-*N,N*-dimethyldibenz[c,f]isoxazolo[2,3-a]-azepine-2-methanamine (comp. 59), was converted into the oxalic acid salt (1:1) in C_2H_5OH at room temperature, yielding 2.6 g (52%) of (±)-*cis*-2,3,3a,8-tetrahydro-*N,N*-dimethyldibenz[c,f]isoxazolo-[2,3-a]azepine-2-methanamine ethanedioate(1:1); mp. 139.5°C (comp. 1).

Example 10

a) Following the same procedure as in example 9, but using 4-methyl-2-pentanone as solvent, there was prepared (±)-*cis*-2,3,3a,8-tetrahydro-2-(1-pyrrolidinyl-methyl)-dibenz[c,f]isoxazolo[2,3-a]azepine ethanedioate(1:1); mp. 167.2°C (comp. 2).

b) Following the same procedure as in example 9, but using tetrahydrofuran as solvent, there was prepared (±)-*cis*-10,11-dichloro-2,3,3a,8-tetrahydro-*N,N*,5-trimethyldibenz[c,f]isoxazolo-[2,3-a]azepine-2-methanamine; mp. 103.2°C (comp. 98).

Example 11

Using the same procedure as in example 9, but stirring the starting materials without solvent in a Parr Pressure Vessel at 100°C overnight, there was prepared (±)-(*cis+trans*)-2,3,3a,8-tetrahydro-*N,N*,3a-trimethyldibenz[c,f]isoxazolo[2,3-a]azepine-2-methanamine (comp. 3).

Example 12

Compound 59 (the free base form of compound 1), as prepared in example 9, was converted to the fumarate salt (1:1) by adding dropwise an ethanolic solution of fumaric acid (0.215 g/ml) to a mixture, cooled on an ice-bath, of the free base form in a mixture of ethanol (8 ml) and diethylether (30 ml). The formed precipitate was filtered off and dried in vacuo, yielding

1 g (71%) of (±)-*cis*-2,3,3a,8-tetrahydro-*N*,*N*-dimethyl-dibenz[c,f]isoxazolo[2,3-a]azepine-2-methanamine (E)-2-butenedioate(1:1); mp. 148.9°C (comp. 4).

Example 13

a) Compound 59 (the free base form of compound 1), as prepared in example 9, was separated andpurified by column chromatography over a Chiralcel OJ column (Daicel, 250 g, 20 µm, length: 23 cm; detection at 200 nm; flow: 40 ml/min; eluent : hexane/ethanol 80/20; injection volume: 25 ml).

1) The desired (A-*cis*)-fractions were collected and the solvent was evaporated. The residue (6.8 g) was dissolved in ethanol (50 ml), stirred at room temperature and converted into the oxalic acid salt (1:1) with a solution of oxalic acid (2.94 g) in ethanol (50 ml). The desired compound crystallized out and the precipitate was filtered off and dried, yielding 5.5 g (24.7%) of (+)-(A-*cis*)-2,3,3a,8-tetrahydro-*N*,*N*-dimethyldibenz[c,f]isoxazolo-[2,3-a]azepine-2-methanamine ethanedioate(1:1); mp. 167.0°C (comp. 5).

2) The desired (B-*cis*)-fractions were treated in an analogous manner as the (A-*cis*)-fractions, yielding 3.4 g (15.2%) of (-)-(B-*cis*)-2,3,3a,8-tetrahydro-*N*,*N*-dimethyl-dibenz-[c,f]isoxazolo[2,3-a]azepine-2-methanamine ethanedioate(1:1); mp. 152.4°C (comp. 6).

b) Compound 1, as prepared in example 9, was separated and purified by column chromatography over a Chiralcel OJ column (Daicel, 250 g, 20 µm, length: 23 cm; detection at 200 nm; flow: 40 ml/min; eluent: hexane/ethanol 80/20;injection: compound 1 (0.55 g) was dissolved in n-hexane/ethanol (1:1) (50 ml); injection volume: 20 ml; concentration: 11.00 mg/ml). Two desired fraction groups (1) and (2) were collected and their solvent was evaporated, yielding 0.2 g (47.5 %) (A-*cis*)-2,3,3a,8-tetrahydro-*N*,*N*-dimethyldibenz[c,f]isoxazolo-[2,3-a]azepine-2-methanamine (comp. 7) and 0.19 g of fraction (2). Fraction (2) contained an impurity (20%) which was separated by reversed-phase column chromatography over RP-Kromasil C-18 (1 inch; eluent: (0.2% NH_4OAc in H_2O)/CH_3OH 30/70). The pure fractions were collected and the organic solvent was evaporated at room temperature. The aqueous residue was extracted with $CHCl_3$. The separated organic layer was evaporated, yielding 0.110 g (26.1%) (B-*cis*)-2,3,3a,8-tetrahydro-*N*,*N*-dimethyldibenz[c,f]isoxazolo-[2,3-a]azepine-2-methanamine (comp. 8).

Example 14

A mixture of (±)-*cis*-2-[(2,3,3a,8-tetrahydrodibenz[c,f]isoxazolo[2,3-a]azepin-2-yl)-methyl]-1*H*-isoindole-1,3(2*H*)-dione (4 g), prepared following the procedure of example 1, and hydrazine hydrate (0.5 ml) in ethanol (80 ml) was stirred at 80°C for 4 hours. The

precipitate was filtered off and purified by open column chromatography over silica gel (eluent : CH_2Cl_2/2-propanone 8/2). The pure fractions were collected and evaporated. The residue (1.6 g) was converted into the oxalic acid salt (1:1) in C_2H_5OH at room temperature. The residue (0.8 g) was purified by column chromatography over silica gel (eluent : CH_2Cl_2/CH_3OH 97.5/2.5 to 95/5). The pure fractions were collected and evaporated, yielding 0.6 g (22%) of (±)-*cis*-2,3,3a,8-tetrahydrodibenz[c,f]isoxazolo-[2,3-a]azepine-2-methanamine (comp. 9).

Example 15

A mixture of (±)-*cis*-2,2,2-trifluoro-*N*-methyl-*N*-[(2,3,3a,8-tetrahydrodibenz[c,f]-isoxazolo[2,3-a]azepin-2-yl)methyl]acetamide (4 g), prepared following the procedure of example 9, and sodium hydroxide (1.06 g) in methanol (60 ml) and water (12 ml) was stirred at 60°C for 3 hours. The solvent was evaporated, the residue was diluted with water and extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4, filtered off and evaporated. The residue (3.9 g) was purified by short open column chromatography over silica gel (eluent : CH_2Cl_2/CH_3OH 95/5). The pure fractions were collected and evaporated. The residue was converted into the oxalic acid salt (1:1) in C_2H_5OH at room temperature, yielding 3.2 g (82%) of (±)-*cis*-2,3,3a,8-tetrahydro-*N*-methyldibenz[c,f]-isoxazolo[2,3-a]azepine-2-methanamine ethanedioate(1:1); mp. 134.0°C (comp. 10).

Example 16

A mixture of intermediate 29 (54.5 g) and *N*,*N*-dimethyl-2-propen-1-amine (35.8 g) in toluene (1000 ml) was stirred overnight at 100 °C. The solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent : CH_2Cl_2/CH_3OH 97/3). The desired fractions were collected and the solvent was evaporated. The residue was purified and separated into its enantiomers by column chromatography over Chiralcel OJ (eluent : hexane/ethanol 90/10). The pure fractions were collected and the solvent was evaporated. The residue was dissolved in ethanol (100 ml; p.a.) and converted into the (S)-malic acid salt (1:1) by addition of (-)-(S)-malic acid (9 g). The mixture was stirred overnight and the resulting precipitate was filtered off, dried, stirred in ethanol (100 ml), washed with DIPE, and dried, yielding 18.8 g of (+)-(A-*cis*)-2,3,3a,8-tetrahydro-*N*,*N*-dimethyldibenz[c,f]isoxazolo[2,3-a]azepinemethanamine (S)-hydroxybutanedioate(1:1); mp. 154.2°C; α=50.41° at 20°C for 100.58 mg in 10 ml methanol (comp. 58).

Example 17

A solution of (+)-(R)-malic acid (0.67 g) in ethanol (10 ml) was added to a solution of compound 59 (1.47 g) in ethanol (10 ml), stirred at room temperature. The resulting

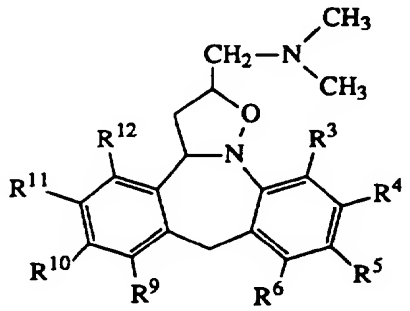
clear solution was allowed to crystallize out. The precipitate was filtered off and dried (vacuum; 50 °C; 24 hours). This fraction was recrystallized from ethanol (15 ml), filtered off and dried (vacuum; 50 °C), yielding 0.76 g (±)-*cis*-2,3,3a,8-tetrahydro-*N*,*N*-dimethyldibenz[c,f]isoxazolo[2,3-a]azepinemethanamine (R)-hydroxybutanedioate (1:1) (35.5%); mp. 138.6°C; α=13.86° at 20°C for 10.10 mg in 10 ml methanol (comp. 57).

Example 18

Compound 58 (2.1 g) was converted into the free base by treatment with aqueous ammonia (at 0 °C). This mixture was extracted with CH_2Cl_2 (100 ml). The separated organic layer was dried, filtered and the filtrate was combined with 3-phenyl-2-(phenylsulfonyl)oxaziridine (1.3 g). This mixture was stirred for 24 hours at room temperature. The solvent was evaporated and the residue was purified by column chromatography over silica gel (eluent : CH_2Cl_2/(CH_3OH/NH_3) 90/10). The pure fractions were collected and the solvent was evaporated. The residue was triturated in DIPE, filtered off and dried, yielding 0.85 g (55%) of (A-cis)-2,3,3a,8-tetrahydro-*N*,*N*-dimethyldibenz[c,f]isoxazolo[2,3-a]azepinemethanamine,*N*-oxide monohydrate; mp. 170°C (comp. 96).

Tables 2 through 6 list compounds that were prepared in a similar way as in one of the hereinabove mentioned examples.

Table 2

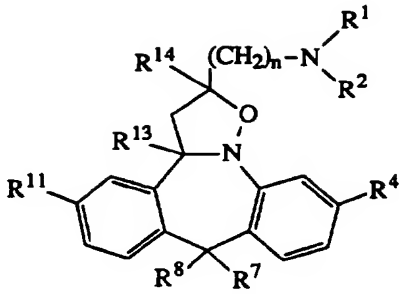


Co No	Ex. No	R^3	R^4	R^5	R^6	R^9	R^{10}	R^{11}	R^{12}	physical data (mp. in °C)
1	9	H	H	H	H	H	H	H	H	(±)-*cis*/$(COOH)_2$/139.5
4	12	H	H	H	H	H	H	H	H	(±)-*cis*/fumaric acid/148.9
5	13b	H	H	H	H	H	H	H	H	(+)-(A-*cis*)/$(COOH)_2$/167.0
6	13b	H	H	H	H	H	H	H	H	(-)-(B-*cis*)/$(COOH)_2$/152.4
7	13a	H	H	H	H	H	H	H	H	(A-*cis*)
8	13a	H	H	H	H	H	H	H	H	(B-*cis*)

Co No	Ex. No	R^3	R^4	R^5	R^6	R^9	R^{10}	R^{11}	R^{12}	physical data (mp. in °C)
57	17	H	H	H	H	H	H	H	H	(-)-*cis*/(R)-malic acid/138.6
58	16	H	H	H	H	H	H	H	H	(+)-(A-*cis*)/(S)-malic acid/ 154.2
59	9	H	H	H	H	H	H	H	H	(±)-*cis*
60	17	H	H	H	H	H	H	H	H	(-)-(A-*cis*)/[R-(R*,R*)]-2,3-bis[(4-methylbenzoyl)oxy]-butanedioic acid/ 155.2
61	13a	H	H	H	H	H	H	H	H	(A-trans)/(S)-malic acid/ 150.9
62	13a	H	H	H	H	H	H	H	H	(B-trans)/(S)-malic acid/ 148.2
11	9	Cl	H	H	H	H	H	H	H	*cis*/(COOH)2/141.9
12	9	H	Cl	H	H	H	H	H	H	±-*cis*/(COOH)2/185.3
13	9	H	H	Cl	H	H	H	H	H	±-*cis*/(COOH)2/172.2
14	9	H	H	H	Cl	H	H	H	H	*cis*/(COOH)2/177.6
63	9	H	H	H	H	Cl	H	H	H	*cis*/(COOH)2/157.5
24	9	H	H	H	H	H	Cl	H	H	*cis*/(COOH)2/171.8
15	9	H	H	H	H	H	H	Cl	H	*cis*/(COOH)2/182.6
16	9	H	Br	H	H	H	H	H	H	*cis*/(COOH)2/170.5
27	9	H	H	Br	H	H	H	H	H	*cis*/181.1
64	9	H	H	Br	H	H	H	H	H	(+)-(A-*cis*)/73.5
65	9	H	H	Br	H	H	H	H	H	(-)-(B-*cis*)/74.1
66	9	H	H	H	Br	H	H	H	H	*cis*/(COOH)2/166.3
67	9	H	H	H	H	Br	H	H	H	*cis*/(COOH)2/158.3
68	9	H	H	H	H	H	Br	H	H	*cis*/(COOH)2/165.0
69	9	H	H	H	H	H	H	Br	H	*cis*/90.2
17	9	CH_3	H	H	H	H	H	H	H	(*cis*+*trans*)/(COOH)2/172.8
18	9	H	CH_3	H	H	H	H	H	H	*cis*/(COOH)2/149.4
19	9	H	H	CH_3	H	H	H	H	H	*cis*/(COOH)2/137.2
70	9	H	H	H	CH_3	H	H	H	H	*cis*/(COOH)2/174.7
20	9	H	H	H	H	CH_3	H	H	H	*cis*/(COOH)2/163.1
21	9	H	H	H	H	H	CH_3	H	H	*cis*/(COOH)2/162.9
22	9	H	H	H	H	H	H	CH_3	H	*cis*/(COOH)2/158.4

Co No	Ex. No	R^3	R^4	R^5	R^6	R^9	R^{10}	R^{11}	R^{12}	physical data (mp. in °C)
23	9	H	H	H	H	H	H	H	CH_3	(*cis*+*trans*)/(COOH)2/189.1
25	9	H	F	H	H	H	H	H	H	*cis*/(COOH)2/172.7
26	9	H	H	F	H	H	H	H	H	*cis*/(COOH)2/157.9
71	9	H	H	H	F	H	H	H	H	*cis*/(COOH)2/175.7
72	9	H	H	H	H	F	H	H	H	*cis*/(COOH)2/151.0
73	9	H	H	H	H	H	F	H	H	*cis*/(COOH)2/157.3
74	9	H	H	H	H	H	H	F	H	*cis*/(COOH)2/171.4
75	9	H	H	H	H	H	H	H	F	*cis*/(COOH)2/190.6
28	9	H	H	H	H	CF_3	H	H	H	*cis*/(COOH)2/165.4
76	9	H	H	H	H	H	CF_3	H	H	*cis*/(COOH)2/168.1
29	9	H	H	H	H	H	H	CF_3	H	*cis*/(COOH)2/170.6
77	9	H	H	H	H	H	H	H	CF_3	*cis*/(COOH)2/176.7
78	9	H	H	H	OCH_3	H	H	H	H	*cis*/(COOH)2/176.9
79	9	H	OCH_3	H	H	H	H	H	H	*cis*/102.2
80	9	H	H	H	H	H	H	OCH_3	H	*cis*/(COOH)2/163.2
81	9	H	H	H	H	H	$N(CH_3)_2$	H	H	*cis*/3/2(COOH)2/114.9
82	9	H	Cl	Cl	H	H	H	H	H	*cis*/110.6
83	9	H	Cl	H	H	Cl	H	H	H	*cis*/malic acid/149.7
84	9	H	Cl	H	H	H	H	Cl	H	*cis*/(COOH)2/196.7
85	9	H	Cl	H	H	Cl	Cl	H	H	cis/(COOH)2/195.0
86	9	H	Cl	H	H	H	Cl	Cl	H	*cis*/(COOH)2/192.6
87	9	H	Cl	F	H	H	H	H	H	*cis*/(COOH)2/264.3
88	9	H	F	H	H	Cl	H	H	H	*cis*/(COOH)2/182.9
89	9	H	F	H	H	H	H	Cl	H	*cis*/(COOH)2/195.7
90	9	H	F	H	H	F	H	H	H	*cis*/(COOH)2/154.9
91	9	H	F	H	H	H	H	F	H	*cis*/(COOH)2/171.1
98	10b	H	Cl	Cl	H	H	H	CH_3	H	*cis*/103.2
99	10b	H	CH_3	CH_3	H	H	H	H	H	*cis*/137.7
100	10b	H	F	F	H	H	H	H	H	*cis*/64.3
101	10b	H	Cl	CH_3	H	H	H	H	H	*cis*/115.6
102	9	H	F	Cl	H	H	H	H	H	*cis*/87.4
103	9	H	H	H	H	H	H	H	H	*trans*
104	9	H	H	H	H	H	H	H	H	*trans* / $(COOH)_2$ (2:3)

Table 3

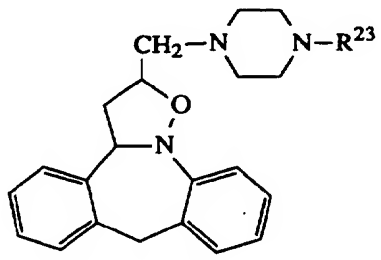


Co. No	Ex No	R^1	R^2	R^4	R^7	R^8	R^{11}	R^{13}	R^{14}	n	phys. data (mp. in °C)
3	11	CH_3	CH_3	H	H	H	H	CH_3	H	1	(*cis+trans*)
9	14	H	H	H	H	H	H	H	H	1	±-*cis*
10	15	H	CH_3	H	H	H	H	H	H	1	±-*cis*/$(COOH)_2$/ 134.0
30	9	CH_3	CH_3	H	H	H	H	H	H	2	±-*cis*/$(COOH)_2$/ 150.1
31	9	CH_3	CH_3	H	H	H	H	H	H	3	±-*cis*/$(COOH)_2$/ 132.7
32	9	CH_3	CH_3	H	H	H	H	H	H	4	±-*cis*/$(COOH)_2$/ 142.9
33	9	C_2H_5	CH_3	H	H	H	H	H	H	1	*cis*/$(COOH)_2$/ 148.4
34	15	$(CH_2)_2$-OH	CH_3	H	H	H	H	H	H	1	±-*cis*/$(COOH)_2$/ 148.6
35	9	C_2H_5	C_2H_5	H	H	H	H	H	H	1	±-*cis*/$(COOH)_2$/ 174.0
36	9	i-C_3H_7	i-C_3H_7	H	H	H	H	H	H	1	±-*cis*/65.8
37	9	$(CH_2)_3$-COOH	CH_3	H	H	H	H	H	H	1	±-*cis*/130.5
38	9	$(CH_2)_4$-COOH	CH_3	H	H	H	H	H	H	1	±-*cis*/155.5
39	9	$(CH_2)_2OCOCH_3$	CH_3	H	H	H	H	H	H	1	±-*cis*/$(COOH)_2$/ 142.6
92	9	$(CH_2)_2OCOCH_3$	CH_3	Cl	H	H	Cl	H	H	1	*cis*/$(COOH)_2$/ 170.5
40	9	CO-CF_3	CH_3	H	H	H	H	H	H	1	±-*cis*/119.1
93	9	CH_3	CH_3	H	CH_3	H	H	H	H	1	$(COOH)_2$/128.1
41	9	CH_3	CH_3	H	CH_3	CH_3	H	H	H	1	*cis*/$(COOH)_2$/ 166.6
42	9	CH_3	CH_3	H	H	H	H	H	CH_3	1	±-*cis*/$(COOH)_2$/ 165.0

Co. No	Ex No	R^1	R^2	R^4	R^7	R^8	R^{11}	R^{13}	R^{14}	n	phys. data (mp. in °C)
43	9	CH_3	CH_3	H	H	H	H	H	CH_3	1	±-*trans*/$(COOH)_2$/ 112.2
94	9	CH_3	CH_3	Cl	H	H	Cl	H	CH_3	1	*cis*/$(COOH)_2$/ 199.2
95	9	CH_3	CH_3	Cl	H	H	Cl	H	CH_3	1	*trans*/67.7
113	9	CH_3	CH_3	H	=CH-CN*		H	H	H	1	(E+Z)/72.9
97	9	CH_3	CH_3	H	$=CH_2$*		H	H	H	1	± / $(COOH)_2$/ 170.0
105	9	$(CH_2)_2OCOCH_3$	CH_3	H	H	H	H	CH_3	H	1	*cis* / $(COOH)_2$ / 125.9
106	9	$(CH_2)_2OCOCH_3$	CH_3	H	H	H	H	CH_3	H	1	*trans* / $(COOH)_2$ / 140.1
107	15	CH_3	H	H	H	H	H	H	H	1	A-*cis* / (S)-malic acid
108	15	CH_3	H	H	H	H	H	H	H	1	B-*cis* / (S)-malic acid
109	9	CH_3	CH_3	H	CH_3	H	H	H	H	1	(2α, 3A α, 8A) / 135.6
110	9	CH_3	CH_3	H	CH_3	H	H	H	H	1	(2α, 3A α, 8B) / 136.3
111	15	CH_3	H	H	H	H	H	H	H	1	*cis*

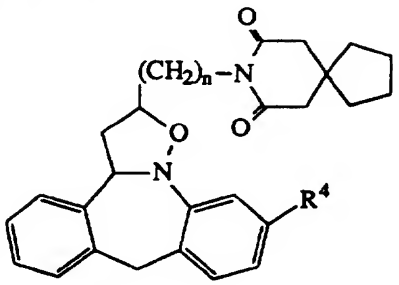
* : R^7 and R^8 are taken together

Table 4



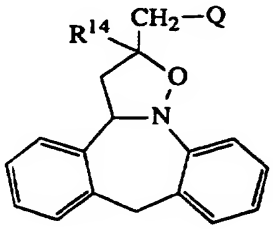
Co. No.	Ex. No.	R^{23}	physical data (mp. in °C)
44	15	H	±-*cis*/$(COOH)_2$/278.9
45	9	CH_3	±-*cis*/$(COOH)_2$/196.6
46	9	CO-CF_3	±-*cis*/$(COOH)_2$/149.4
47	9	3-chlorophenyl	±-*cis*/59.1
112	9	1,1-diphenylmethyl	*cis*

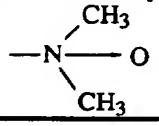
Table 5



Co. No.	Ex. No.	R^4	n	physical data (mp. in °C)
48	9	H	1	±-*cis*/150.8
49	9	F	1	*cis*/74.7
50	9	H	2	±-*cis*/190.0
51	9	H	4	±-*cis*

Table 6



Co. No.	Ex. No.	R^{14}	Q	physical data (mp. in °C)
2	10a	H	1-pyrrolidinyl	*cis*/$(COOH)_2$/167.2
52	9	H	1-piperidinyl	±-*cis*/$(COOH)_2$/198.8
53	9	CN	1-piperidinyl	±-*trans*/127.8
54	9	H	hexahydro-1*H*-azepin-1-yl	±-*cis*/$(COOH)_2$/188.0
55	9	H	1,3-dihydro-2*H*-isoindol-2-yl	±-*cis*/150.0
56	9	H	1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl	±-*cis*/184.1
96	18	H		(A-*cis*)

C. Pharmacological example

Example 19 : "mCPP Test on Rats"

Rats were treated with the test compound at a dose varying between 0.0025 mg/kg and 40 mg/kg body weight, at pre-test time T varying between 5 and 480 minutes, and with 1 mg/kg mCPP (metachlorophenylpiperazine), injected intravenously, 15 minutes prior to the test. After pre-test time T elapsed, treated rats were submitted to the "Open Field Test on Rats" as described in Drug Dev. Res. 18, 119-144 (1989), but using an infra-red light source instead of a Kleverlux® (12V/20W) light source. A dose at which 40 % of the tested rats showed suppression of the mCPP induced effects, i.e. mCPP-antagonism, was defined as an active dose. The activity range of a test compound was measured by the ratio of the HAD (highest active dose) over the LAD (lowest active dose). The compounds with number 1, 4-7, 10, 15, 18, 25, 26, 30, 39, 57, 58, 77, 84, 89 and 91 had a ratio (HAD over LAD) of 16 or more at a pre-test time T being 60 minutes. Also at a pre-test time T of 60 minutes, the compounds with number 2, 8, 11-14, 16, 19, 21, 23, 24, 27, 29, 35, 42-45, 47, 48, 52, 54, 55, 59-62, 65-75, 78, 79, 87, 88, 90 and 92-94 showed mCPP-antagonism at least at one tested dose.

Example 20 : *In vitro* binding affinity for 5-HT_{2A} and 5-HT_{2C} receptors

The interaction of the compounds of formula (I) with 5-HT_{2A} and 5-HT_{2C} receptors was assessed in *in vitro* radioligand binding experiments.

In general, a low concentration of a radioligand with a high binding affinity for the receptor is incubated with a sample of a tissue preparation enriched in a particular receptor (1 to 5 mg tissue) in a buffered medium (0.2 to 5 ml). During the incubation, the radioligands bind to the receptor. When equilibrium of binding is reached, the receptor bound radioactivity is separated from the non-bound radioactivity, and the receptor bound activity is counted. The interaction of the test compounds with the receptors is assessed in competition binding experiments. Various concentrations of the test compound are added to the incubation mixture containing the tissue preparation and the radioligand. Binding of the radioligand will be inhibited by the test compound in proportion to its binding affinity and its concentration.

The radioligand used for 5-HT_{2A} binding affinity is ^{3}H-ketanserin and the tissue used is the frontal cortex of the rat. The compounds with number 1-5, 7, 9, 10, 12-14, 16-20, 27, 30, 31, 33-35, 39, 42, 45, 52, 54, 57-59, 62-64, 67, 68, 70-72, 74, 77, 79, 82, 84, 87, 88, 89, 91, 96, 97, 100, 101 and 108 produced an inhibition of the 5-HT_{2A} receptor of more than 40 % at a test concentration of 10^{-8} M. The compounds with number 6, 8, 22, 32, 36-38, 43, 46, 55, 61, 65, 76, 80, 86, 92-94, 98, 99, 105 and 107 produced an inhibition of the 5-HT_{2A} receptor of more than 40 % at a test

concentration of 10^{-7} M. The other compounds were either not tested or produced an inhibition of the 5-HT_{2A} receptor of less than 40 % at a test concentration of 10^{-7} M. The radioligand used for 5-HT_{2C} binding affinity is ^{3}H-mesulergine and the tissue used is the choroid plexus of the pig. The compounds with number 1-3, 5, 7, 9-19, 21, 22, 24-27, 29, 30, 33-35, 42, 52, 54, 57-59, 64, 66, 68, 70-72, 74, 77, 79, 80, 82, 84, 86-93, 96, 98, 100, 101 and 108 produced an inhibition of the 5-HT_{2C} receptor of more than 40 % at a test concentration of 10^{-8} M. The compounds with compound number 4, 6, 8, 20, 23, 31, 32, 38, 39, 41, 45, 55, 61-63, 65, 67, 75, 76, 81, 94, 95, 99, 107 and 113 produced an inhibition of the 5-HT_{2C} receptor of more than 40 % at a test concentration of 10^{-7} M. The other compounds were either not tested or produced an inhibition of the 5-HT_{2C} receptor of less than 40 % at a test concentration of 10^{-7} M.

D. Composition examples

"Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I), a pharmaceutically acceptable acid addition salt, a stereochemically isomeric form thereof or a *N*-oxide form thereof.

Example 21 : ORAL DROPS

500 Grams of the A.I. was dissolved in 0.5 l of 2-hydroxypropanoic acid and 1.5 l of the polyethylene glycol at 60~80°C. After cooling to 30~40°C there were added 35 l of polyethylene glycol and the mixture was stirred well. Then there was added a solution of 1750 grams of sodium saccharin in 2.5 l of purified water and while stirring there were added 2.5 l of cocoa flavor and polyethylene glycol q.s. to a volume of 50 l, providing an oral drop solution comprising 10 mg/ml of A.I. The resulting solution was filled into suitable containers.

Example 22 : ORAL SOLUTION

9 Grams of methyl 4-hydroxybenzoate and 1 gram of propyl 4-hydroxybenzoate were dissolved in 4 l of boiling purified water. In 3 l of this solution were dissolved first 10 grams of 2,3-dihydroxybutanedioic acid and thereafter 20 grams of the A.I. The latter solution was combined with the remaining part of the former solution and 12 l 1,2,3-propanetriol and 3 l of sorbitol 70% solution were added thereto. 40 Grams of sodium saccharin were dissolved in 0.5 l of water and 2 ml of raspberry and 2 ml of gooseberry essence were added. The latter solution was combined with the former, water was added q.s. to a volume of 20 l providing an oral solution comprising 5 mg of the active ingredient per teaspoonful (5 ml). The resulting solution was filled in suitable containers.

Example 23 : FILM-COATED TABLETS

Preparation of tablet core

A mixture of 100 grams of the A.I., 570 grams lactose and 200 grams starch was mixed well and thereafter humidified with a solution of 5 grams sodium dodecyl sulfate and 10 grams polyvinylpyrrolidone in about 200 ml of water. The wet powder mixture was sieved, dried and sieved again. Then there was added 100 grams microcrystalline cellulose and 15 grams hydrogenated vegetable oil. The whole was mixed well and compressed into tablets, giving 10.000 tablets, each containing 10 mg of the active ingredient.

Coating

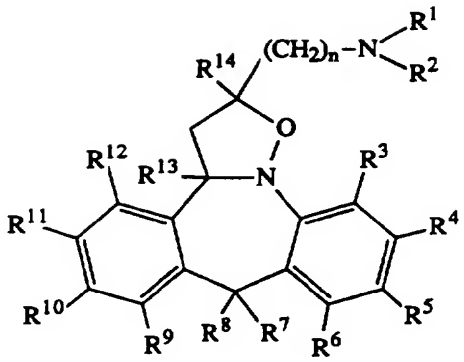
To a solution of 10 grams methyl cellulose in 75 ml of denaturated ethanol there was added a solution of 5 grams of ethyl cellulose in 150 ml of dichloromethane. Then there were added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 Grams of polyethylene glycol was molten and dissolved in 75 ml of dichloromethane. The latter solution was added to the former and then there were added 2.5 grams of magnesium octadecanoate, 5 grams of polyvinylpyrrolidone and 30 ml of concentrated colour suspension and the whole was homogenated. The tablet cores were coated with the thus obtained mixture in a coating apparatus.

Example 24 : INJECTABLE SOLUTION

1.8 Grams methyl 4-hydroxybenzoate and 0.2 grams propyl 4-hydroxybenzoate were dissolved in about 0.5 l of boiling water for injection. After cooling to about 50°C there were added while stirring 4 grams lactic acid, 0.05 grams propylene glycol and 4 grams of the A.I.. The solution was cooled to room temperature and supplemented with water for injection q.s. ad 1 l, giving a solution comprising 4 mg/ml of A.I.. The solution was sterilized by filtration and filled in sterile containers.

Claims

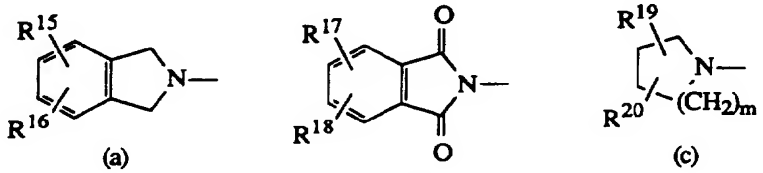
1. A compound of formula



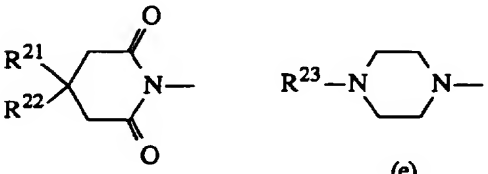
(I)

a pharmaceutically acceptable acid or base addition salt or a stereochemically isomeric form thereof, and also the *N*-oxide forms thereof, wherein :

R^1 and R^2 each independently are hydrogen; C_{1-6}alkyl; C_{1-6}alkylcarbonyl; trihalomethylcarbonyl; C_{1-6}alkyl substituted with hydroxy, C_{1-6}alkyloxy, carboxyl, C_{1-6}alkylcarbonyloxy, C_{1-6}alkyloxycarbonyl or aryl; or R^1 and R^2 taken together with the nitrogen atom to which they are attached may form a morpholinyl ring or a radical of formula :



(a) (b) (c)



(d) (e)

wherein :

R^{15}, R^{16}, R^{17} and R^{18} each independently are hydrogen, halo, trifluoromethyl, or C_{1-6}alkyl;

m is 1, 2, or 3;

R^{19}, R^{20}, R^{21} and R^{22} each independently are hydrogen, or C_{1-6}alkyl; or R^{21} and R^{22} taken together may form a bivalent radical C_{4-5}alkanediyl;

R^{23} is hydrogen; C_{1-6}alkyl; C_{1-6}alkylcarbonyl; trihalomethylcarbonyl; C_{1-6}alkyloxycarbonyl; aryl; di(aryl)methyl; C_{1-6}alkyl substituted with hydroxy, C_{1-6}alkyloxy, carboxyl, C_{1-6}alkylcarbonyloxy, C_{1-6}alkyloxycarbonyl or aryl;

R^3, R^4, R^5, R^6, R^9, R^{10}, R^{11} and R^{12} each independently are hydrogen, halo, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, carboxyl, nitro, amino, mono- or di(C_{1-6}alkyl)amino, C_{1-6}alkylcarbonylamino, aminosulfonyl, mono- or di(C_{1-6}alkyl)aminosulfonyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl;

R^7 and R^8 each independently are hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy or R^7 and R^8 taken together may form mono- or di(cyano)methylene; a bivalent radical of formula $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-O-(CH_2)_2-O-$, $-O-(CH_2)_3-O-$; or, together with the carbon atom to which they are attached, a carbonyl; or

R^7 and R^8 taken together may form methylene;

R^{13} is hydrogen, C_{1-6}alkyl or trifluoromethyl;

R^{14} is hydrogen, C_{1-6}alkyl, cyano or trifluoromethyl;

n is zero, 1, 2, 3, 4, 5, or 6;

aryl is phenyl; or phenyl substituted with 1, 2 or 3 substituents selected from halo, hydroxy, C_{1-6}alkyl and trifluoromethyl.

2. A compound according to claim 1, wherein R^7 and R^8 each independently are hydrogen or methyl, or wherein R^7 and R^8 are taken together to form methylene or cyanomethylene.

3. A compound according to claim 2, wherein R^{13} is hydrogen or methyl.

4. A compound according to claim 3, wherein R^{14} is hydrogen, cyano or methyl.

5. A compound according to claim 4, wherein the aromatic substituents R^4, R^5 and R^{11} each independently are selected from hydrogen, fluoro, chloro, bromo, methyl or trifluoromethyl; the remaining aromatic substituents being hydrogen.

6. A compound according to claim 5, wherein n is 1 or 2, R^1 is hydrogen or methyl and R^2 is methyl.

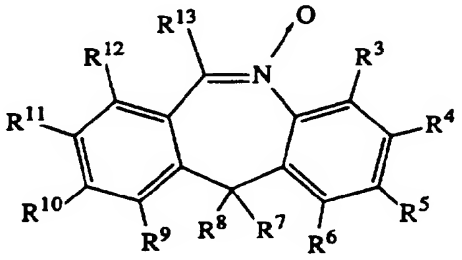
7. A compound according to claim 1, wherein the compound is *cis*-2,3,3a,8-tetrahydro-*N*,*N*-dimethyldibenz[c,f]isoxazolo[2,3-a]azepine-2-methanamine; or *cis*-2,3,3a,8-tetrahydro-*N*-methyldibenz[c,f]isoxazolo[2,3-a]azepine-2-methanamine, the stereochemically isomeric forms thereof and their pharmaceutically acceptable acid addition salts, and also their *N*-oxide forms.

8. A composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound as claimed in any one of claims 1 to 7.

9. A process of preparing a composition as claimed in claim 8, wherein a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as claimed in any one of claims 1 to 7.

10. Use of a compound as claimed in any one of claims 1 to 7 as a medicine.

11. A compound of formula

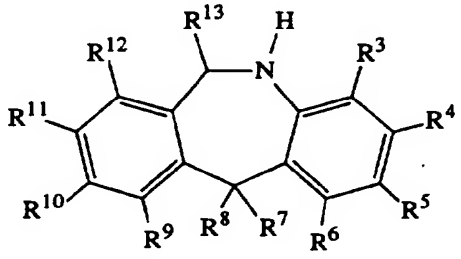


(II)

wherein R^3 to R^{13} are defined as in claim 1, an acid or base addition salt thereof or a stereochemically isomeric form thereof.

12. A process of preparing a compound as claimed in claim 11, characterized in that :

an intermediate of formula (IV) wherein R^3 to R^{13} are defined as in claim 1, is oxidized with a suitable oxidizing agent.

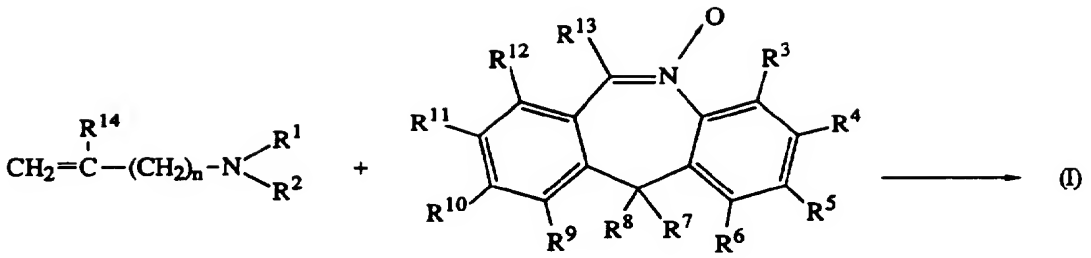


(II)

(IV)

13. A process of preparing a compound as claimed in claim 1, characterized in that :

a) a dienophile of formula (III) is reacted with an intermediate of formula (II) :



(III) (II) (I)

wherein in the intermediates (II) and (III) R^1 to R^{14} and n are defined as in claim 1;

b) converting compounds of formula (I) into each other following art-known transformations, and further, if desired, converting the compounds of formula (I), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a therapeutically active non-toxic base addition salt by treatment with a base, or conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and, if desired, preparing stereochemically isomeric forms or *N*-oxide forms thereof.

INTERNATIONAL SEARCH REPORT

Inter ..al Application No
PCT/EP 95/04196

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D498/04 A61K31/535 //(C07D498/04,261:00,223:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 17, 1980 PROVO US, pages 341-350, R.B. MOFFETT 'Tetracyclic heterocycles as CNS agents' see compound 59 see page 349, column 2 ---	11,12
A	US,A,4 039 558 (VAN DER BURG WILLEM JACOB ET AL) 2 August 1977 cited in the application ---	1-10
A	EP,A,0 421 823 (SANKYO CO) 10 April 1991 cited in the application -----	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 January 1996	-7. 02. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	De Jong, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

[1.]ational application No.
PCT/EP 95/04196

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 10 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inter ial Application No
PCT/EP 95/04196

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		BE-A-	834902	27-04-76
		CA-A-	1082182	22-07-80
		DE-A-	2548045	06-05-76
		FR-A,B	2289198	28-05-76
		GB-A-	1530299	25-10-78
		JP-A-	51068598	14-06-76
		SE-A-	7511968	29-04-76
EP-A-0421823	10-04-91	CA-A-	2026925	06-04-91
		CN-A-	1051360	15-05-91
		EP-A-	0505014	23-09-92
		NO-B-	175781	29-08-94
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